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EXAMINER	
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1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/570,909	HOPF, CARSTEN	
	Examiner	Art Unit	
	KEVIN K. HILL	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 December 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *7-11* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *7-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *Aug. 17 and Dec. 18, 2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on December 18, 2007 has been entered.

Applicant had elected with traverse the invention of Group I, claim(s) 7-11, drawn to a method for identifying a gamma-secretase and/or a beta secretase modulator, and a method for preparing a pharmaceutical composition for the treatment of neurodegenerative diseases, wherein the agent that modulates a gamma-secretase.

Claims 7-11 are under consideration.

Priority

This application is a 371 of PCT/EP04/09771, filed September 2, 2004. Acknowledgment is made of Applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d). Certified copies of the following foreign applications have been provided:

EPO 03019642.2, filed September 5, 2003,
PCT/EP2003/013980, filed December 10, 2003,
EPO 04001895.4, filed January 29, 2004,
EPO 04001894.7, filed January 29, 2004,
EPO 04007447.8, filed March 26, 2004,
PCT/EP2004/004891, filed May 7, 2004,
PCT/EP2004/004889, filed May 7, 2004, and
EPO 04018874.0, filed August 9, 2004.

Response to Amendment

Applicant has provided to the Examiner locations in EPO 03019642.2, filed September 5, 2003, that support the instant invention. Accordingly, the effective priority date of the instant application is granted as September 5, 2003.

Information Disclosure Statement

Applicant has filed an Information Disclosure Statement (IDS) on August 17, 2007 and two copies of an IDS on December 18, 2007, providing 281 references. The Examiner was able to consider these to the extent of time allowable.

The second copy of the IDS filed December 18, 2007 is lined through for being a duplicate.

Citations BC (WO 01/49871) and BE (WO 01/70993) in the IDS filed August 17, 2007 is lined through because the Examiner has already entered this into the record in the Office Action mailed January 9, 2007.

Citation CY (CHO, 1999) in the IDS filed December 18, 2007 is lined through for being a duplicate of CA in the IDS filed August 17, 2007.

The signed and initialed PTO Forms 1449 are mailed with this action.

Examiner's Note

Unless otherwise indicated, previous rejections that have been rendered moot in view of the amendment will not be reiterated. The arguments in the July 9, 2007 response will be addressed to the extent that they apply to current rejection(s).

Specification

Sequence compliance

37 CFR 1.821(d) states: "[w]here the description or claims of a patent application discuss a sequence that is set forth in the "Sequence Listing" in accordance with paragraph (c) of this section, reference must be made to the sequence by use of the sequence identifier, preceded by "SEQ ID NO:" in the text of the description of claims, even if the sequence is also embedded in the text or the description or claims of the patent application.

1. **The disclosure is objected to for the following reason:** this application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 because sequences are set forth in the specification that lack sequence identifiers.

Applicant's attention is drawn, in particular, to the following locations in the instant specification: pg 18, ¶4 and pg 377, ¶2.

Sequences must be assigned a SEQ ID NO. Sequences must be provided in computer readable format (CRF) and on paper. Further, a statement indicating the two formats are the same must also be provided.

It is often convenient to identify sequences in figures by amending the Brief Description of the Drawings section (see MPEP 244.02). If the sequences are already present in the sequence listing, it would be remedial to amend the Brief Description of the Drawings or specification to include the appropriate sequence identifiers. Applicants are required to comply with all of the requirements of 37 CFR 1.821 - 1.825. Any response to this office action that fails to meet all of these requirements will be considered non-responsive.

The nature of the noncompliance with the requirements of 37 C.F.R. 1.821 through 1.825 did not preclude the examination of the application on the merits, the results of which are communicated below.

Claim Objections

2. **Claims 7 and 11 are objected to because of the following informalities:** Periods exist after steps (a) and (b), e.g. "a).". While there is no set statutory form for claims, the present Office practice is to insist that each claim must be the object of a sentence starting with "I (or we) claim," "The invention claimed is" (or the equivalent). If, at the time of allowance, the quoted terminology is not present, it is inserted by the Office of Patent Publication. Each claim begins with a capital letter and ends with a period. Periods may not be used elsewhere in the claims except for abbreviations. See *Fressola v. Manbeck*, 36 USPQ2d 1211 (D.D.C. 1995). Where a claim sets forth a plurality of elements or steps, each element or step of the claim should be separated by a line indentation. See 37 CFR 1.75(i).

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the Applicant regards as his invention.

3. **Claims 7-11 are rejected under 35 U.S.C. 112, second paragraph**, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

Claims 7 and 11 (and dependent claims) are vague in that no step(s) in the claimed method refers back to or recapitulates the preamble of the claim. Applicants recite a method of identifying a gamma-secretase modulator comprising the step of identifying a FADS2-interacting molecule, but no step is recited that actually accomplishes the preamble. It is unclear if additional, undisclosed steps are a part of the claimed method and therefore the metes and bounds of the claimed subject matter are unclear. Dependent claims are included in the basis of the rejection because although they recite and encompass the method of identifying a gamma secretase modulator, they do not clarify the nature of when the inventive method has been completed.

Furthermore, it is unclear if additional, unrecited steps are necessary and must be performed to formulate the gamma secretase modulator into a pharmaceutical composition for the treatment of neurodegenerative disease.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. **Claims 7-11 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement.** The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claimed invention is directed to a method of identifying a gamma-secretase modulator comprising the step of identifying a FADS2-interacting molecule. At issue for the

purpose of written description requirements is the lack of adequate written description for the genus of FADS2 molecules and variants thereof possessing the newly disclosed biological activity of interacting with one or more components of the gamma-secretase complex, such that a molecule that binds to FADS2 or a variant thereof and is both an inhibitor of FADS2 activity and a modulator, e.g. agonist or antagonist, of gamma-secretase activity that affects the ability of APP to be cleaved.

> *Vas-cath Inc. v. Mahurkar*, 19USPQ2d 1111, clearly states that Applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification should "clearly allow persons of ordinary skill in the art to recognize that (he or she) invented what is claimed." (See *Vas-cath* at page 1116).

The disclosure of a single species is rarely, if ever, sufficient to describe a broad genus, particularly when the specification fails to describe the features of that genus, even in passing. (see *In re Shokal* 113USPQ283(CCPA1957); *Purdue Pharma L.P. vs Faulding Inc.* 56 USPQ2nd 1481 (CAFC 2000).

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of compete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof.

In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been described by their complete structure. Fatty acid delta-6 desaturase (FADS2) has been known in the art to catalyze the rate-limiting step in the biosynthesis of polyunsaturated fatty acids (PUFA), as disclosed in the instant specification (pg 4, ¶1). However, Applicant appears to have discovered a novel biological activity of FADS2 using a FADS2 protein as shown in SEQ ID NO:76. However, the specification discloses that the term "FADS2" does not only mean the protein as shown in SEQ

ID NO:76, but also a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant encoded by a nucleic acid that hybridizes to the nucleic acid encoding SEQ ID NO:76 (pg 4, ¶4), and the specification does not disclose the portion(s) of wildtype FADS2 (SEQ ID NO:76) are responsible for manifesting the interaction between FADS2 and members of the gamma-secretase complex so as to affect gamma-secretase activity upon the cleavage of APP as postulated. Thus, the method embraces the use of an enormous genus of structurally undisclosed variants of FADS2/FADS2-like polypeptides that not necessarily possess the newly disclosed biological activity of interacting with one or more members of the gamma-secretase complex.

The Revised Interim Guidelines state:

"The claimed invention as a whole may not be adequately described if the claims require an essential or critical element which is not adequately described in the specification and which is not conventional in the art" (col. 3, page 71434), "when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus", "in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus" (col. 2, page 71436).

An Applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997).

Possession may also be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the Applicant was in possession of the claimed invention. See, e.g., *Pfaff v.*

Wells Elecs., Inc., 525 U.S. 55, 68, 1 19 S.Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998), *Regents of the University of California v. Eli Lilly*, 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997)*, *Amgen, Inc. v. Chugai Pharmaceutical*, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991) (one must define a compound by "whatever characteristics sufficiently distinguish it").

Therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. See *Fiers v. Revel*, 25 USPQ2d 1602 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016. One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483. *In Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Without a correlation between structure and function, the claim does little more than define the claimed invention by function. That is not sufficient to satisfy the written description requirement. *See Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406 ("definition by function … does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is").

Applicant has not provided any description or reduction to practice of a method for identifying a gamma-secretase modulator comprising the step of identifying a FADS2-interacting molecule by determining whether the given test compound binds to FADS2 and modulates gamma-secretase activity to cleave APP. Based on the Applicant's specification, the skilled artisan cannot envision the detailed chemical structure of the enormous genus of FADS2 and variants thereof test proteins that are capable of enhancing or suppressing the activity of gamma-secretase to cleave APP when bound to a structurally undisclosed compound that binds to and inhibit at least one FADS2 activity, as encompassed by the claims.

The inventive concept is Applicant's apparent discovery of an interaction between FADS2 and members of the gamma-secretase complex. Thus, the artisan is dependent upon

Applicant's disclosure to reveal that part of FADS2 activity responsible for modulating gamma-secretase activity, as measured by APP cleavage, for example.

Accordingly, given that the specification does not teach what is the complete structure of a single species of the exceptionally broadly-defined FADS2 genus, this limited information is not deemed sufficient to reasonably convey to one skilled in the art that the Applicant is in possession of the required starting materials, that is functional variants or derivatives of FADS2, to perform the necessary active steps and effect the claimed method, at the time the application was filed.

Given that there is no evidence of the screening method to have been performed (claims 7-10), it necessarily follows that there is no evidence for a method of preparing a pharmaceutical compound for the treatment of a neurodegenerative disease (claim 11), the method comprising formulating a gamma-secretase modulator identified as per the identifying method.

Thus, for the reasons outlined above, it is concluded that the claims do not meet the requirements for written description under 35 U.S.C. 112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

5. **Claims 7-11 are rejected under 35 U.S.C. 112, first paragraph**, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The instant specification does not reasonably provide enablement for methods for identifying compounds useful in modulating a biological activity of an enormous genus of FADS2 polypeptides or variants thereof, and their ability to interact with components of the gamma-secretase complex, wherein the modulatory compound is capable of modulating the ability of gamma-secretase to cleave APP, nor methods of formulating pharmaceutical compositions comprising said modulatory agent(s).

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention. If not, whether an artisan would have required undue experimentation to make and use the claimed invention and

whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue" (In re Wands, 858 F.2d 731, 737, 8 USPQ2ds 1400, 1404 (Fed. Cir. 1988)). Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification. Therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of the invention. And thus, skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

The Breadth of the Claims and The Nature of the Invention

The claims are broad for encompassing an enormous genus of FADS2 and FADS2-like polypeptide indicator compositions, and the ability of this genus of polypeptides to modulate gamma-secretase activity when bound by structurally undisclosed compounds, wherein the term "modulator" is understood to mean agents that can either enhance or suppress gamma secretase activity. The breadth of the claims reasonably embraces *in vitro*, *ex vivo* and *in vivo* settings in which to perform the claimed screening method.

The inventive concept in the instant application is the observation that FADS2 (SEQ ID NO:76) appears to interact with components of the gamma-secretase complex, e.g. Nicastrin and Presenilin 2, that participates in the cleavage of APP, and that by using siRNA to decrease the expression of FADS2 in cultured neural cells, the production of Aβ1-42 peptide could be reduced (pg 378, lines 4-9). Given the role that aberrant cleavage of APP plays in Alzheimer's disease, it is desirable to understand how the interactions between FADS2 and the gamma-secretase complex is regulated, where FADS2 and gamma-secretase component protein(s) interaction(s) occurs, and whether FADS2 can regulate gamma-secretase activity. In particular, Applicant's preferred embodiment is to identify compounds that inhibit FADS2 activity, and thereby inhibit gamma-secretase activity (pg 21, ¶3; claim 9).

The Existence of Working Examples and The Amount of Direction Provided by the Inventor

The specification discloses that an siRNA-mediated knockdown of FADS2 expression in SKNBE2 neuroblastoma cells or H4 neuroglioma cells attenuates the secretion of Aβ1-42 (pg 365, Figures 3A and 3B). By inhibiting FADS2 expression using siRNA, the production of Aβ1-42 peptide could be reduced in these tissue cultured cells (pg 378, lines 4-9).

The specification discloses that by using the technique of tandem affinity purification with FADS2 (pg 374, Example 4), Applicant appears to have identified peptides corresponding to components of the gamma-secretase complex, indicating a possible physical interaction between FADS2 and one or more members of gamma-secretase.

Applicant contemplates the screening method(s) may be practiced *in vitro*, on solid supports (pg 27, ¶5), in a cell (pg 28, ¶1), and animals (pg 33, ¶2). However, there are no working examples demonstrating that a compound that binds to FADS2 is capable of also modulating the activity of gamma-secretase, e.g. to increase or decrease the cleavage of APP.

Despite the disclosed association between FADS2 and components of the gamma-secretase complex, there are no working examples validating that any compound identified by the claimed method(s) would, in fact, be useful in treating the enormous genus of neurodegenerative diseases contemplated by Applicants.

Applicant appears to have discovered a novel biological activity of FADS2. However, the specification does not disclose what FADS2 amino acid sequences of the FADS2/FADS2-like polypeptides are both necessary and sufficient to fulfill the required functional properties, e.g. interacting with one or more members of the gamma-secretase complex so as to enhance or suppress gamma-secretase activity to cleave APP, such that when this FADS2/FADS2-like domain is bound to an exogenous compound, the FADS2/FADS2-like polypeptide would necessarily increase or decrease gamma-secretase activity.

The State of the Prior Art, The Level of One of Ordinary Skill and The Level of Predictability in the Art

Applicant's discovery, and basis for the claimed method, is due to observations from the use of a gene-silencing, siRNA molecule targeted against FADS2. However, one of ordinary skill in the art would readily recognize that an antisense molecule does not anticipate the entire

breadth of the contemplated 'modulator' compound genus embraced by the instant invention because the antisense RNA does not bind to FADS2 to effect modulation of gamma-secretase activity as required by the claims. Rather, the antisense affects whether or not the FADS2 RNA transcript is translated into protein.

With respect to the use of antisense molecules, at the time the instant invention was filed, the art recognized significant unpredictability to equate phenotypes derived from antisense technology with phenotypes derived from true loss-of-function methods. According to Stein (Stein, C.A., Pharmacology and Therapeutics 85: 231-236, 2000):

> "[A]ntisense oligonucleotide biotechnology has entered a phase of its development in which many problems engendered by non-sequence specificity are being recognized and being actively addressed. However, in order to improve specificity of the methodology, attention must now also be aid to co-suppression of gene activity due to irrelevant cleavage." Stein further states that "[T]o the extent that this issue also is addressed, correlations between the down-regulation of a defined target and an observed biological outcome (e.g., growth suppression) *eventually* [*emphasis added*] may be possible." (page 235, Concluding remarks)

Stein also teaches (Stein, C.A., September, J. Clinical Investigation 108(5): 641-644, 2001) that:

> "serious question have arisen as to whether an observed biological effect in an antisense experiment has indeed been produce by an antisense mechanism, or whether it is due to a complex combination of non-sequence specific effects. Investigators must therefore understand how to employ antisense technology properly and should recognize its limitations" (page 641, column 1, paragraph 2). However, in many, and perhaps most of the citations in which only a single oligomer was evaluated, the results reported may represent some combination of true antisense effects with sequence-nonspecific and cytotoxic effects" (page 642, column 1, lines 20-25). Except under rare and strongly justified circumstances, the use of an observed biological endpoint to claim antisense efficacy is not acceptable (page 642, column 2, lines 6-10).

Similarly, Caplen (Caplen, N.J., August, Gene Therapy 11(16): 1241-1248, 2004) reviews the progress and prospects of RNA interference methods triggered by double-stranded RNA. While RNAi appears to be easy to induce, critical analysis of RNAi derived phenotypic data should not be overlooked. The validation of the RNAi effect in mammalian cells is important and that non-specific effects of RNAi need to be carefully assessed in mammalian cells (page 1245). For example, "ensuring the specificity and quantifying the efficacy of the particular siRNA or shRNA against a clinically relevant target transcript is essential in justifying its further development." And, as Stein taught above (2001), Caplen states "it should be possible to rescue the functional phenotype induced by RNAi by expression of a transcript resistant to the siRNA under study."

With respect to inhibitors of FADS2, the art teaches that FADS2 inhibitors cause a decrease in the synthesis of arachidonic acid (AA), docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) (Harmon et al, Lipids 38:469-476, 2003). The art also teaches that decreased amounts of DHA and EPA are inversely correlated with the prevalence of Alzheimer's disease. Conquer et al (Lipids 35(12):1305-1312, 2000) teach that the diversity in the fatty acid composition of brain phospholipids (PL) may influence the biophysical properties of membrane lipids including, for example, fluidity properties and charge. Optimal functioning of membrane proteins of the neuron depends on membrane potential, receptor occupancy, phosphorylation-dependent intermolecular associations, and protein and lipid composition. In neurons, synaptosomes have the highest concentration of long-chain polyunsaturated fatty acids (PUFA), including DHA and AA. The exact function of these PUFA is not clear although AA is the main substrate for synthesis of various eicosanoid mediators and DHA appears to exert a role in membrane fluidity and long-term potentiation, a process that is necessary for memory function. Membrane destabilization, due to a loss of potentially important unsaturated fatty acids, may contribute to Alzheimer's disease (AD) pathogenesis or it may facilitate the deposition of the neuro- toxic amyloid β-protein from APP cleavage (pg 1305, col. 2, ¶2).

Recent studies suggest that dietary intake of fish, the most important source of long-chain n-3 fatty acids such as 20:5n-3 (EPA) and DHA, is inversely correlated with the development of dementia, and in particular Alzheimer's disease, in Western countries. Furthermore, decreased

DHA levels in the plasma PC of elderly individuals may be predictive of the development of AD after 10 years. These results, coupled with the results of earlier studies showing decreased levels of DHA in the brain of individuals with AD, as well as papers suggesting a link between decreased levels of DHA in serum and various neurologic pathologies, suggest that plasma levels of DHA, and possibly other n-3 fatty acids, may be lower in the plasma of AD patients as well as patients with other dementias (pg 1308, col. 2).

Furthermore, Lim et al (J. Neuroscience 25(12):3032-3040, 2005) teach that, in an Alzheimer's disease model, increasing dietary consumption of DHA modulates APP processing by decreasing α- and β-APP C-terminal fragments, and that DHA could be protective against β-amyloid production, accumulation and potential downstream toxicity (pg 3032, Abstract).

The discovery of a possible interaction between FADS2 and one or more components of the gamma-secretase complex is novel. Thus, the art is silent with respect to cell-free, cell-based and multicellular organism-based methods of assaying the ability of FADS2 to interact with and regulate gamma-secretase activities. However, neither the specification nor the pre-and post-filing art teach the full scope of FADS2 and/or gamma-secretase activities so that one of ordinary skill in the art could recognize that changes in FADS2 activity would necessarily modulate gamma-secretase activity. Rather, one of ordinary skill in the art would reasonably expect a compound that inhibits FADS2 activity, Applicant's preferred embodiment, would not predictably inhibit gamma-secretase activity or be useful for the treatment of a neurological disorder such as Alzheimer's disease because the inhibition of FADS2 activity would be reasonably expected to cause a decrease in the amount of AA, EPA and DHA in the membrane of neurons, thus impairing neural membrane function, facilitating Aβ deposition, and thus phenocopy the physiological states observed in AD patients.

The Quantity of Any Necessary Experimentation to Make or Use the Invention

FADS2 (SEQ ID NO:76) is 386 amino acids in length. While methods of isolating or generating variants of a polypeptide were known in the art at the time of the invention, it was not routine in the art to screen - by a trial and error process - for all polypeptide variants having a

substantial number of modifications as encompassed by the claims for those polypeptides having the desired newly disclosed activity and utility.

Thus, the quantity of necessary experimentation to make or use the invention as claimed, based upon what is known in the art and what has been disclosed in the specification, will create an undue burden for a person of ordinary skill in the art to demonstrate that the enormous genus of FADS2 polypeptide variants inherently possesses the functional properties of modulating gamma-secretase activity, wherein the enormous genus of FADS2 polypeptide variants may be used in a method to identify compounds that, upon binding to said genus of FADS2 variants, will necessarily increase and/or decrease gamma-secretase activity, wherein such activities can be assayed in cell-free methods, e.g. *in vitro* or on supportive substrates, or *in vivo*, e.g. in a cell or organism, so as to reliably detect modulations in the interaction between the enormous genus of FADS2/FADS2-like polypeptides and one or more members of the gamma-secretase complex, and wherein the FADS-binding compound would be useful in a pharmaceutical formualtion for the treatment of a neurodegenerative disease. The artisan would essentially have to invent for themselves each of the recited assays to measure the claimed activities under the appropriate conditions.

Accordingly, the instant claims are rejected for failing to comply with the enablement requirement.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

6. **The prior rejection of Claims 7-11 under 35 U.S.C. 103(a)** as being unpatentable over Winther et al (WO 01/70993 A2, September 27, 2001) and Fechteler et al (WO 01/49871 A2, July 12, 2001) **is withdrawn**. In response to Applicant's request that the Examiner point to specific evidence in the record to support the finding that the interaction between FADS2 and members of the gamma secretase holoenzyme was general knowledge in the prior art, the Examiner appears to have misinterpreted the acronym 'FAD' used in the prior art to indicate FADS2, whereupon further consideration of said prior art the FAD acronym more correctly meant Familial Alzheimer's Disease. Applicant's additional arguments have been considered but are moot in view of the new ground(s) of rejection.

7. **Claims 7-11 are rejected under 35 U.S.C. 103(a)** as being unpatentable over Fechteler et al (WO 01/49871 A2, July 12, 2001; *of record) in view of Winther et al (WO 01/70993 A2, September 27, 2001; *of record), Conquer et al (Lipids 35(12):1305-1312, 2000) and Nakada et al (NeuroReport 1:153-155, 1990).

The claims are drawn to a method for identifying a gamma secretase modulator, comprising the steps of identifying a FADS2-interacting molecule, wherein the FADS2-interacting molecule binds to, and inhibits FADS2, and determining whether the FADS2-interacting molecule is capable of modulating gamma secretase, as measured by the ability of amyloid precursor protein (APP) to be cleaved.

Determining the scope and contents of the prior art.

Fechteler et al disclose methods of finding inhibitors of membrane-based proteases, in particular gamma secretase (pg 1, [0002]; pg 4, [0062]). The compounds identified by the inventive method(s) are contemplated to be useful for the treatment of neurodegenerative disorders, e.g. Alzheimer's disease, Parkinson's disease and Huntington's chorea (pg 4, [0065]). The activity of gamma-secretase may be measured by the ability of gamma-secretase to cleave a reporter protein that comprises a fragment of amyloid β, specifically the C99 fragment (pg 3, [0040-0044]), or endogenous Aβ polypeptides (pg 8, [0113-0114], Example 8).

Fechteler et al do not disclose the method step of identifying a FADS2-interacting molecule by determining whether a given test compound binds to FADS2. However, at the time of the invention, Winther et al disclosed a method for identifying a compound that inhibits the activity of delta-6-desaturase (also known in the art as FADS2, see pg 4, line 1 of the instant specification) (pg 3, [0028]). Winther et al disclosed that host systems in which the method(s) may be performed include *in vivo* and *in vitro* systems (pgs 14-15, [0166-1076]). Winther et al contemplated that potential agonists include small molecules that bind to FADS2 polypeptides, and thereby extinguish its activity, by prevent binding to cellular binding molecules, e.g. regions of FADS2 which contact other proteins and/or localize the FADS2 within a cell, and regions which bind substrate, such that normal activity is prevented (pgs 17-18, [0201-0204]). Winther et al disclose a composition for the treatment of a lipid metabolism disorder, comprising a compound identified by the inventive method and a pharmaceutically acceptable carrier (pg 3, [0031]), wherein contemplated disorders include neurodegenerative diseases such as Alzheimer's disease and diabetic neuropathy (pg 4, [0037]).

Ascertaining the differences between the prior art and the claims at issue, and Resolving the level of ordinary skill in the pertinent art.

People of the ordinary skill in the art will be highly educated individuals, such as medical doctors, scientists, or engineers possessing advanced degrees, including M.D.'s and Ph.D.'s. Thus, these people most likely will be knowledgeable and well-read in the relevant literature and have the practical experience in lipid biosynthetic pathways and homeostasis, neurobiology and pathology of neurodegenerative diseases, molecular biology and methods of screening chemical compounds. Therefore, the level of ordinary skill in this art is high.

At the time of filing of the instant application, those of ordinary skill in the art were aware of screening methods to identify compounds that modulate gamma-secretase activity to cleave APP, and screening methods to identify compounds that inhibit FADS2 activity. The ordinary artisan possessed the knowledge that the prevalence of Alzheimer's disease was positively correlated with aberrant APP cleavage patterns and inversely correlated with decreased amounts of DHA and EPA (Conquer et al), and that inhibition of FADS2 causes a decrease in the synthesis of arachidonic acid, docosahexaenoic acid and eicosapentaenoic acid. Changes in fatty acid composition, especially those in polyunsaturated fatty acids synthesized, in part, by FADS2 have long been known to have several fundamental effects on cell membranes, including membrane fluidity, phase transition temperature, and lipid-protein interaction. Alteration in fatty acid composition of brain membrane is believed to directly indicate alteration in membrane phospholipid metabolism. The most striking abnormalities are consistently high levels of 18:2 (n-6), a substrate of FADS2, strongly indicating abnormalities in delta-6 desaturase (FADS2) in Alzheimer's brain. Therefore, it is plausible that the abnormalities in fatty acid composition in Alzheimer's disease may account for some of the biochemical abnormalities reported in Alzheimer's disease (Nakada et al, pg 154, col.s 1-2, joining ¶). Thus, the fatty acid composition of brain phospholipids (PL) may influence the biophysical properties of membrane lipids and membrane protein function, e.g. gamma-secretase responsible for proper and aberrant APP cleavage.

Considering objective evidence present in the application indicating obviousness or nonobviousness.

It would have been obvious to one of ordinary skill in the art to try determining whether a FADS2-interacting molecule is capable of modulating gamma-secretase activity to cleave APP with a reasonable chance of success because the prior art recognized an association between FADS2 activity and the synthesis of membrane fatty acids, and that decreased levels of arachidonic acid, docosahexaenoic acid and eicosapentaenoic acid would be reasonably expected to affect activity of membrane proteins, e.g. gamma-secretase. Furthermore, there are only three possible outcomes regarding the potential ability of an FADS2-interacting molecule to modulate gamma-secretase activity that can be easily determined in a single assay: enhancement,

suppression, or no effect. An artisan would be motivated to try determining whether a FADS2-interacting molecule is capable of modulating gamma-secretase activity to cleave APP because Conquer et al suggest that it remains to be tested whether decreased levels of n-3 fatty acids in the plasma and/or brain of patients with AD—an effect mimicked by FADS2 inhibitors—contributes to disease symptoms, or whether they were only a biochemical change that occurs alongside those other changes responsible for disease symptoms (Conquer et al; pg 1310, col. 1, last ¶), e.g. aberrant APP cleavage as taught by Fechteler et al.

Thus, absent evidence to the contrary, the invention as a whole is *prima facie* obvious.

Conclusion

8. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to KEVIN K. HILL whose telephone number is (571)272-8036. The Examiner can normally be reached on Monday through Friday, between 9:00am-6:00pm EST.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Joseph T. Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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